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Effects of direct current stimulation on synaptic plasticity in a single neuron

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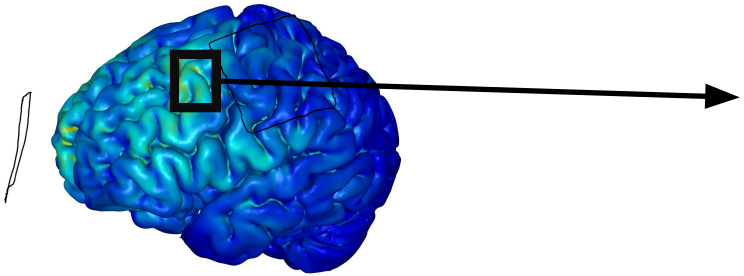
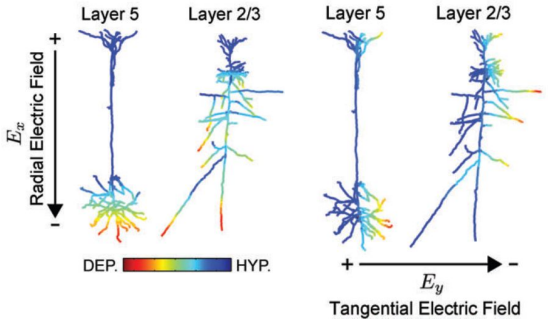
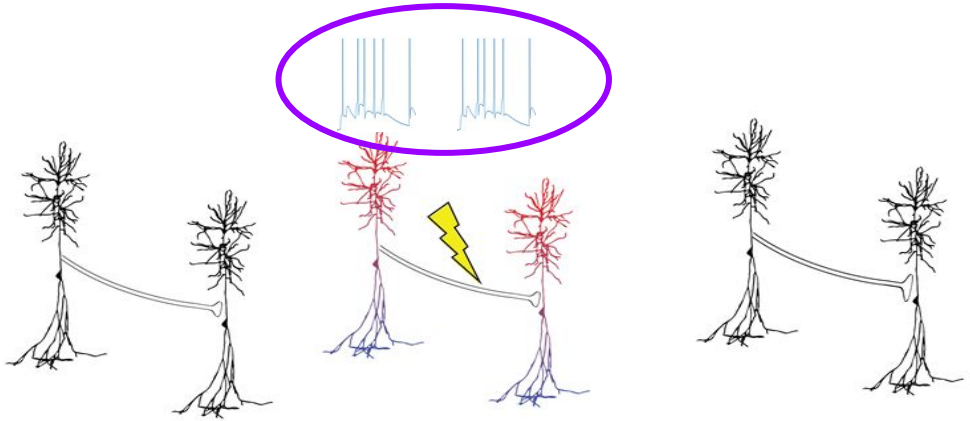
Transcranial Direct Current Stimulation (tDCS)





Rahman et al., 2013

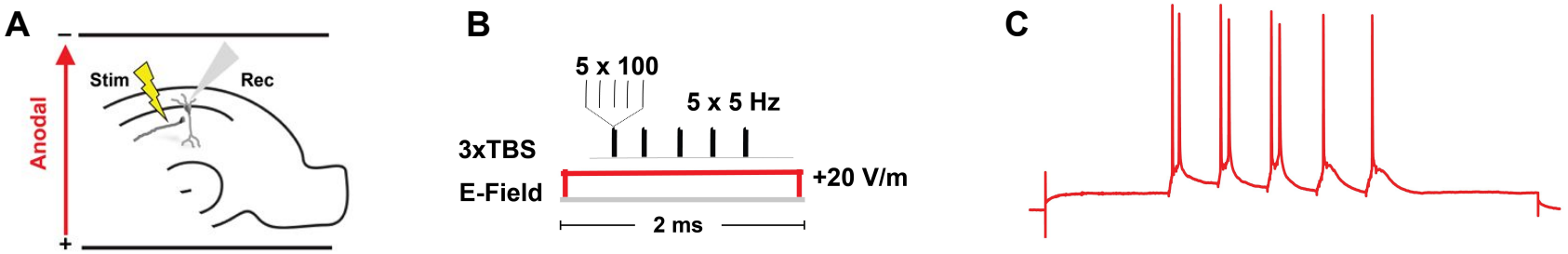
DCS is known to affect synaptic long-term potentiation (LTP) in vitro. How?



Hypothesis:

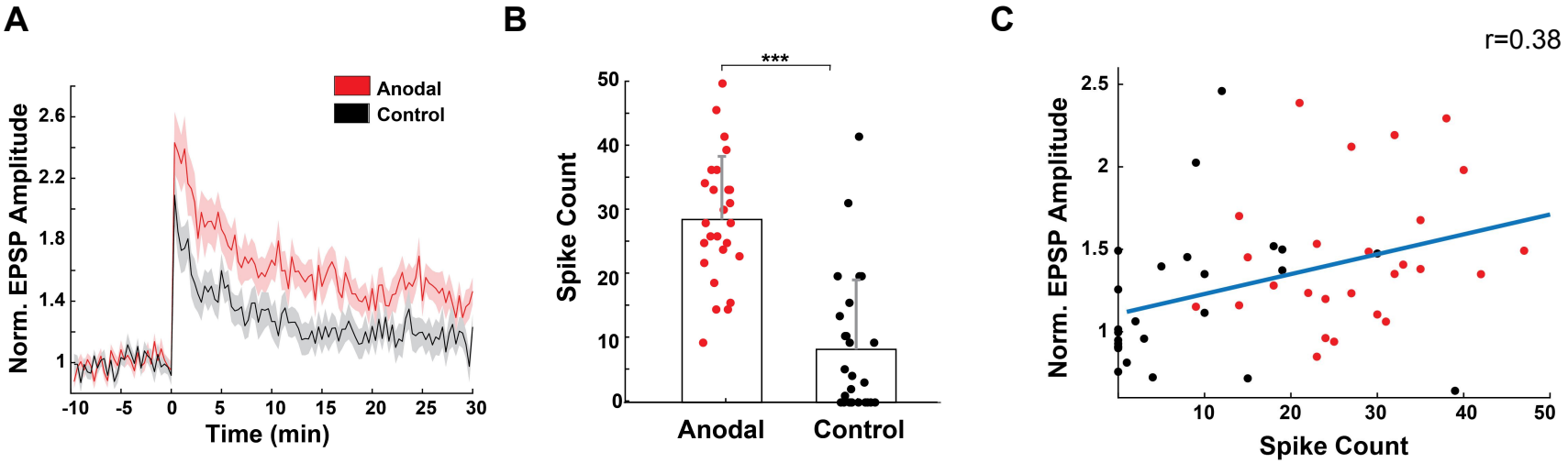
DCS increases of somatic polarization in the postsynaptic neuron → increases the somatic spiking → boost TBS-induced LTP

Experimental Design:



A: Experimental configuration with whole-cell somatic patch-clamp recording and stimulation of Schaffer-Collateral fibers in the presence of an electric field (red) caused by anodal DCS. **B:** TBS pulse pattern. TBS: 5 pulses at the frequency of 100 Hz were repeated 5 times at the frequency of 5 Hz. TBS was repeated three times with the time interval of 30 seconds. **C:** A sample trace during plasticity induction

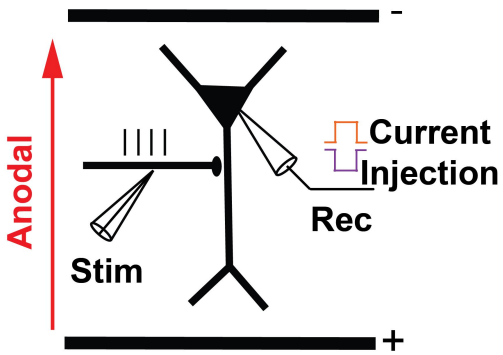
Results:

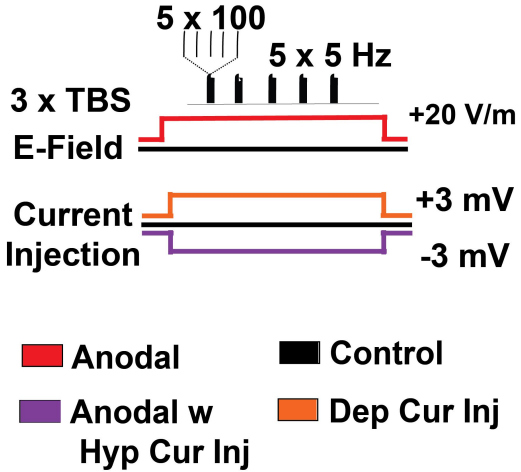


A: Normalized EPSP amplitude. **B:** Number of spikes during theta burst stimulation. **C.** Normalized EPSP amplitude vs. spike count. * p<0.05, **p<0.01, *** p<0.001

Causality?

- Current injection
  - Emulate: injecting a positive current to depolarize the soma
  - Abolish: DCS while injecting a negative current

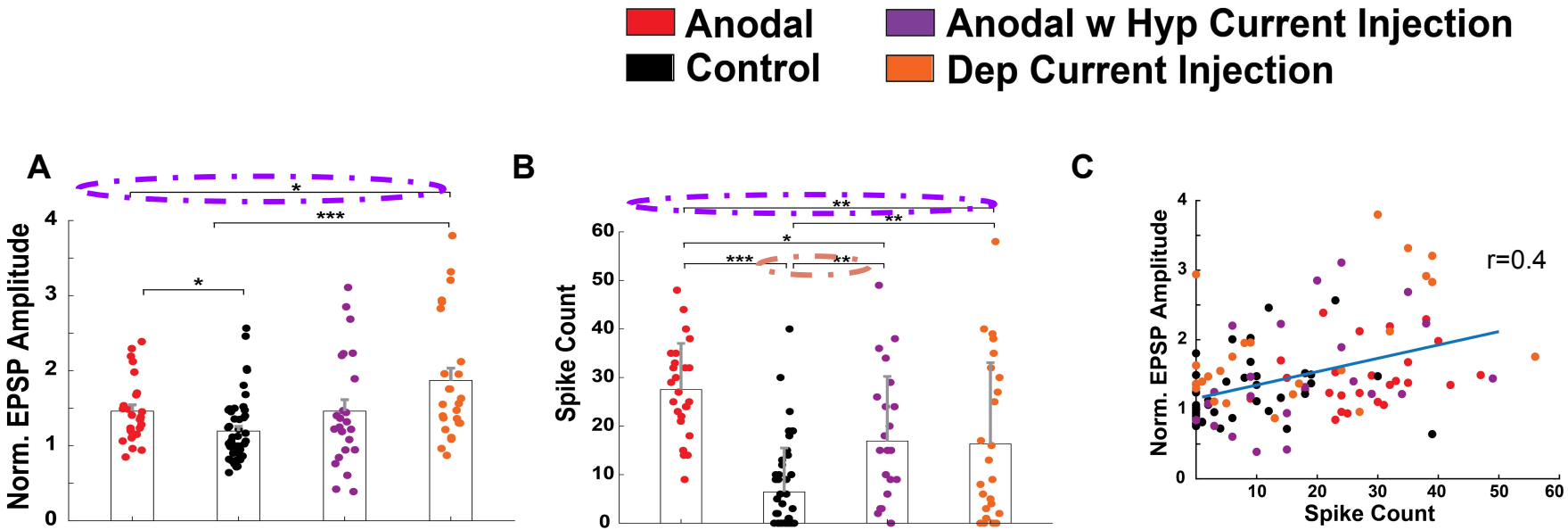




Earlier studies: 0.15 mv per 1V/m electric field

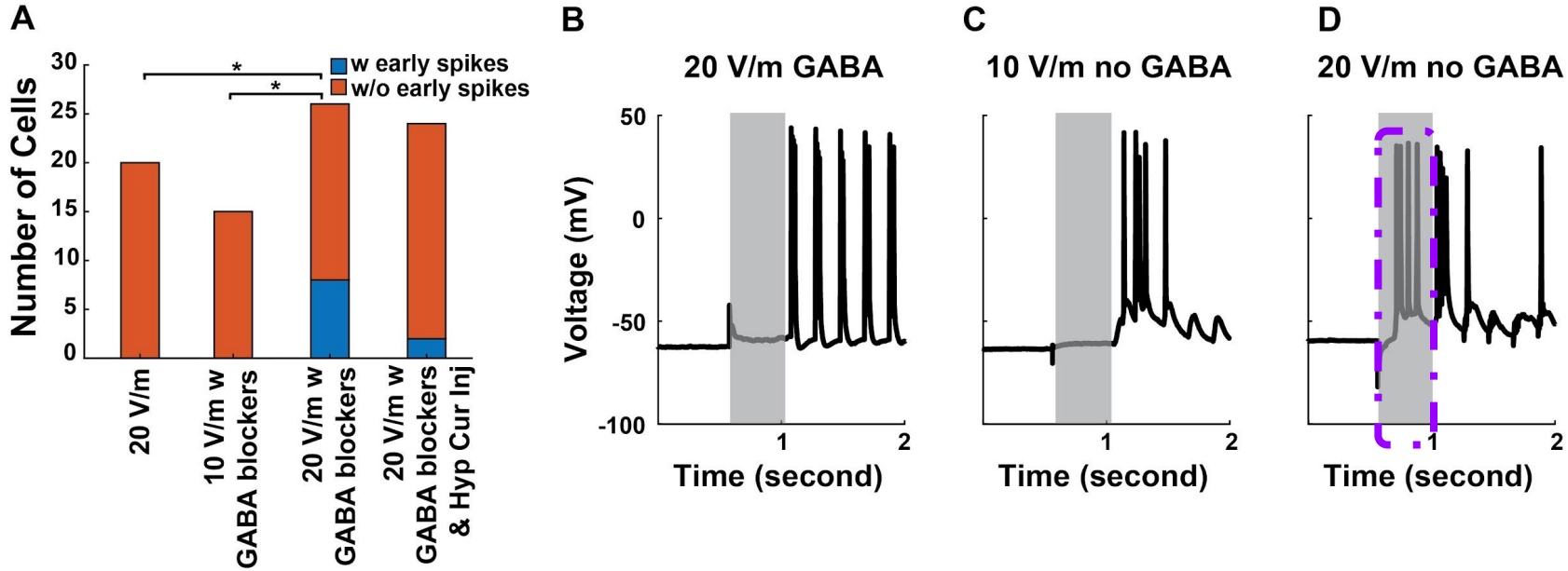
Radman et al. 2009 Brain Stim.; Berzhanskaya et al 2013 J. Comput Neurosci.

A: Experimental setup. **B:** Illustration of induction protocol



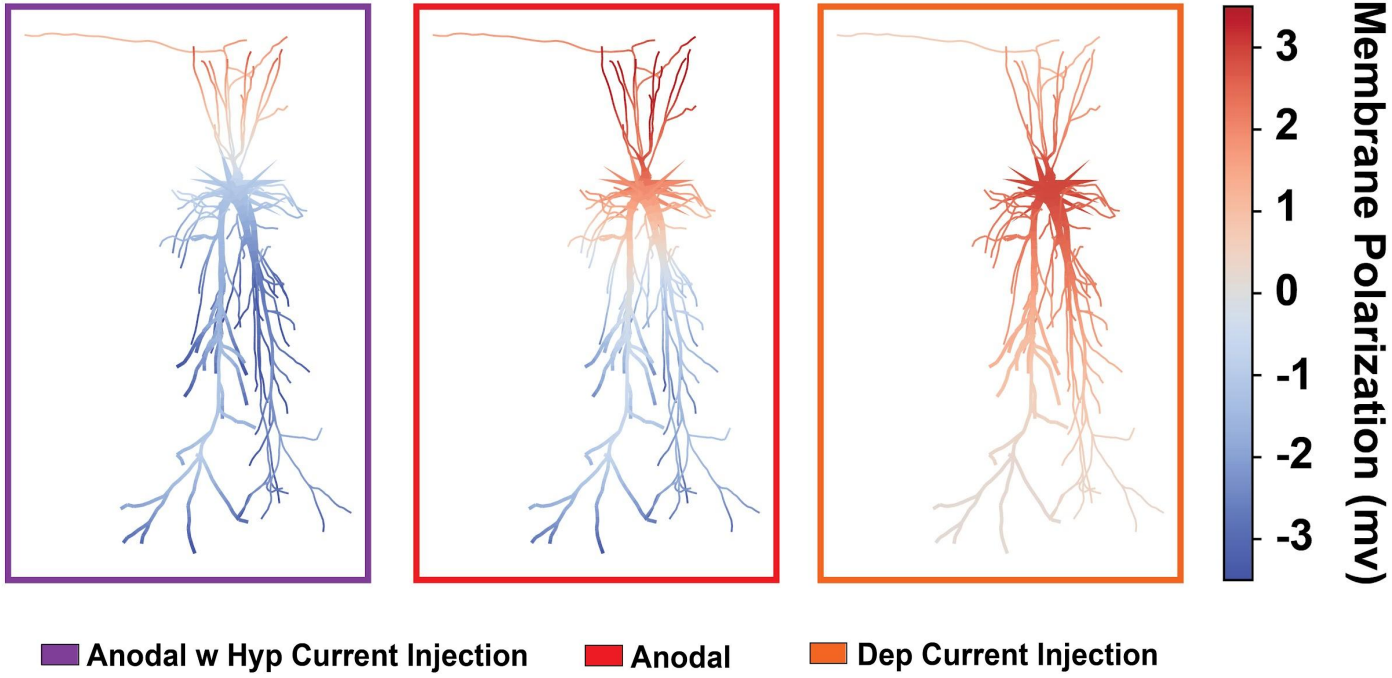
A: Traces of average normalized EPSP amplitude. **B:** Normalized EPSP amplitude in different conditions: anodal (N=26 cells), control (N=48 cells), anodal with hyperpolarizing somatic current injection (N=24 cells), and depolarizing somatic current injection (N=25 cells). **C:** Positive correlation of LTP with somatic spiking across all cells and experimental conditions. Using a linear mixed effect model, we found an effect of spike count ($p=8.9 \times 10^{-7}$)

DCS evoked network activity



A: Number of cells exhibiting action potentials before TBS onset. Fisher exact test with FDR. *p<0.05 (20V/m vs. 20 V/m with GABA blocker) and *p<0.05 (10V/m with GABAblocker vs. 20 V/m with GABA blocker). **B:** firing was evoked by a stimulator while GABAergic inputs were intact under 20 V/m electric field (N=20 cells). The gray area shows the period prior to TBS and after DCS onset. **C:** firing was evoked by a stimulator under 10 V/m when GABA antagonists were added. **D:** neuronal firing was evoked by a stimulator electrode under 20 V/m electrode when GABA antagonists were added.

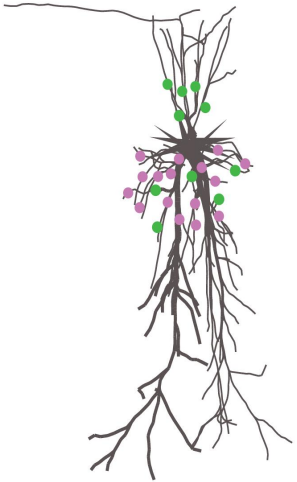
Computational modeling



Membrane polarization with somatic current injection in a multicompartment neuronal model. Left: Somatic hyperpolarizing current injection with anodal DCS, Middle: anodal DCS, Right: Somatic depolarizing current injection

Computational modeling

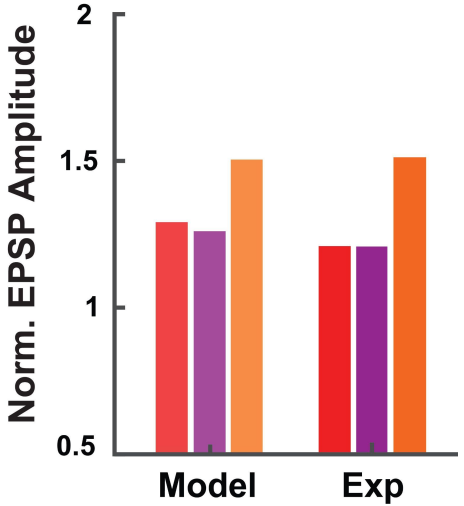
A



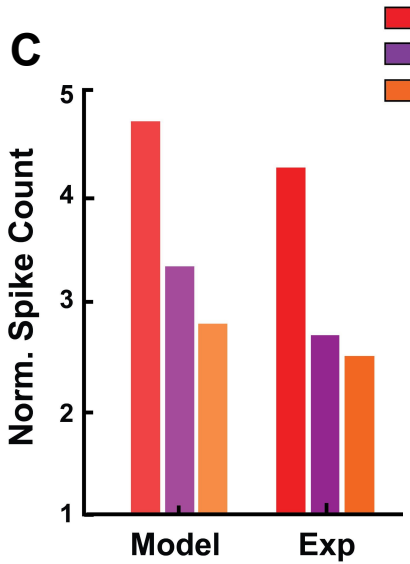
Synapses stimulated by TBS

Synapses stimulated by spontaneous network activity due to DCS

B



C



A: Simulated biophysically realistic CA1 pyramidal neuron with synapses stimulated by applied TBS (pink) and synapses stimulated by spontaneous network activity due to DCS (green). **B:** For experiments this shows the normalized EPSP amplitude relative to control condition. For models this shows the normalized synaptic efficacy relative to control condition. **C:** Normalized spike count relative to control condition in single-neuron model and experiment (Exp)

Summary

- We found that TBS-induced LTP was enhanced when paired with anodal DCS as well as depolarizing current injections.
- In both cases, somatic spiking during the TBS was increased, suggesting that evoked somatic activity is indeed the primary factor affecting LTP modulation. However, the boost of LTP with DCS was less than expected given the increase in spiking activity alone.
- In some cells, we also observed spontaneous somatic spiking during DCS, suggesting that DCS also modulates LTP via spontaneous network activity.
- The computational model reproduces the observed effects of DCS on LTP and suggests that these effects are driven by both direct changes in postsynaptic spiking and indirect changes due to network activity.
- DCS enhances synaptic plasticity by increasing postsynaptic somatic spiking, but we also find that an increase in network activity may limit this enhancement.

Thanks to